UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY, and MANULIFE INSURANCE COMPANY (f/k/a INVESTORS PARTNER INSURANCE COMPANY), Plaintiffs, vs. ABBOTT LABORATORIES, Defendant.	Civil Action No. 05-11150-DPW Hon. Judge Douglas P. Woodlock

CORRECTIONS TO THE AFFIDAVIT OF JAMES THOMAS

Abbott Laboratories ("Abbott") respectfully submits these corrections to the Affidavit of James Thomas. Exhibit 534 was inadvertently referred to in the affidavit as Exhibit 603. The affidavit has been corrected to include references to Exhibit 534 instead of Exhibit 603 and is attached. Abbott is also attaching a true and correct copy of Exhibit 534 with the correct cover sheet. This is the only correction to the Affidavit of James Thomas. Abbott will provide the court with courtesy copies of Mr. Thomas' affidavit with these corrections on Tuesday, March 11, 2008.

Dated: March 10, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By its attorneys

/s/ Jeffrey I. Weinberger
Jeffrey I. Weinberger

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Counsel for Abbott Laboratories

CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on March 10, 2008.

Date: March 10, 2008.

/s/ Ozge Guzelsu

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY, Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF JAMES THOMAS

I, James Thomas, hereby declare and say:

1. My name is James Thomas. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

Education and Professional Background

2. I am currently employed by Abbott Laboratories ("Abbott") as a manager in Statistics. I became employed by Abbott in 1995.

3. I received a B.S. in Statistics and an M.S. in Statistics from Brigham Young University in 1989 and 1991, respectively.

4. Prior to joining Abbott in 1995, I worked as a statistician at Parexel International, a contract research organization ("CRO"), for approximately three and a half years. In 1995, I joined Abbott as an Associate Statistician. I remained in that position until 2000 or 2001, when I was promoted to Senior Statistician I. In approximately 2003, I was promoted to Senior Statistician II, a position I occupied until I was appointed in 2005 to my current position as Manager of Statistics.

5. During my employment as an Abbott Senior Statistician I and II, and as Manager of Statistics, I have been responsible for helping to design clinical trials of compounds in Phase II and Phase III of development, for reviewing clinical trial protocols, case report forms, and clinical study reports. As Senior Statistician II and Manager of Statistics, I have also been responsible for supervising other Abbott statisticians.

6. Throughout my employment at Abbott, I have also been responsible from time to time for helping to prepare reports for Abbott's management regarding the status of Abbott's clinical trials and regarding the clinical trials of compounds that have been or are being developed by Abbott's competitors in the pharmaceutical industry. Abbott regularly obtains detailed information about the clinical trials of competitors' compounds from publicly available sources, including articles in scientific journals. In order to fulfill my responsibilities at Abbott, it is necessary for me to remain current on developments in statistical issues in clinical trials at Abbott and at competitors, and I do so by participating in meetings and presentations at Abbott at which such developments are presented and discussed and by reading Abbott clinical study reports and journal articles and other publicly available sources of information.

7. During my employment as a statistician at Abbott, I have worked on approximately 25 Phase II and Phase III clinical trials for compounds in development by Abbott.

ABT-594

8. ABT-594 is an analgesic compound that was under development in the Analgesia Venture at Abbott from 1997 through October 2001. I worked as a statistician on ABT-594 during this period. ABT-594 is a member of a class of compounds known as cholergenic channel modulators ("CCM") or neuronic nicotinic receptors ("NNR"). My responsibilities with regard to ABT-594 included consulting with the clinical team in the design of Phase II clinical trials and in the development of the protocols for each of the Phase II clinical trials, preparing sections of each of the protocols (especially those sections dealing with statistical matters), developing and supervising the analyses for the final clinical study report, and writing sections of the clinical study report.

9. I participated in the preparation of the Protocol and the final Clinical Study Report for the ABT-594 M99-114 Phase IIb clinical trial. Attached hereto as Exhibits 534 and 795, respectively, are true and correct copies of the Protocol and the Clinical Study Report.

10. My work on each of the ABT-594 clinical trials included the calculation of the planned power of the trials. I did not choose what the planned power of the trials should be. That was a decision made by the ABT-594 clinical team.

11. The original planned power of the M99-114 trial was 80%. However, in my experience at Abbott it was not unusual for clinical trials such as the ABT-594 Phase II clinical trials to be designed at different levels of planned power. In my experience,

Abbott sometimes sets planned power of its Phase II trials at 80%, but at other times Abbott sets planned power at less than 80%. For example, in three ABT-594 Phase II studies other than the M99-114 trial discussed above, Abbott designed each trial to have less than 80% planned power. For a Phase II Osteoarthritis Pain trial, M98-826, which was a 256 patient, randomized, double-blind, placebo-controlled trial, the planned power of the trial was 56%. The planned power of the Neuropathic Pain trial, M98-833, a 133 patient, randomized, double-blind, placebo-controlled, multiple dose trial, was also 56%. For the Molar Extraction study, M97-772, a 290 patient, randomized, double-blind, placebo-controlled, single dose trial, the planned power was 70%. Attached hereto as Exhibits MI, MJ, and MK are true and correct copies of the clinical protocols of each of these three trials.

12. I am also aware that Abbott has planned the power of Phase III clinical trials at less than 70%. For example, I worked approximately ten years ago on the design and protocol of a Phase III trial for the compound now known as Depakote, an Abbott drug for the treatment of several indications, including bipolar disorder and epilepsy. For this Phase III trial, the Abbott Depakote clinical team selected a power of 70%.

13. In 2000, after Abbott had begun enrolling patients in the M99-114 clinical trial, I was asked to calculate, in a fully blinded manner, the effect of smaller sample sizes on the probability of detecting the M99-114's predefined standardized treatment effect of 0.46. My calculations in this regard assumed that all patients would be evaluable for efficacy. Attached hereto as Exhibit 573 is an email dated September 28, 2000, from me to Ms. Rebecca L. Brown containing an example of such power calculations. I was also asked to consider the effect on the power of the study of smaller sample sizes on the

probability of detecting standardized treatment effects smaller and larger than 0.46. Attached hereto as Exhibit 566 is a true and correct copy of an email dated August 29, 2000, from me to Ms. Catherine K. Kacos, containing an example of such calculations.

Early Terminations of Patients From Trials of Pain Compounds

14. Before the M99-114 study was unblinded, I did not regard the early termination rate or the proportion of early terminations for adverse events to be necessarily a problem for the potential success of the study or the compound. In studies for some types of compounds, an early termination rate of close to 50% of patients enrolled in a clinical pain trial, as was experienced in the ABT-594 M99-114 trial, is not inappropriate or unexpected. Specifically, based on my experience at Abbott and my review of publicly available information, I was aware in 2000 and 2001 that early termination rates for clinical trials of some types of pain compounds in particular can be in the range of 40 to 60%, and sometimes higher. I was also aware that many compounds for the treatment of chronic pain, including many opioids, have experienced high rates of early terminations in clinical trials, yet are widely considered to be effective for a variety of different types of chronic pain and have been approved by the FDA. Based on my experience, these facts are well-known at Abbott and in the pharmaceutical industry generally.

15. In late 2000 and in 2001, I was aware from my work at Abbott that clinical trials of tramadol, controlled release codeine, and controlled release oxycodone, among other pain compounds, had shown that the compounds were efficacious despite experiencing dropout rates ranging from one-third to more than half of the total number of patients enrolled in the trial. For example, an article in the *Archives of Internal Medicine* reported in 2000 that 52.6% of the patients enrolled in a double-blinded, placebo-controlled trial

of controlled release oxycodone discontinued their participation in the study, and that 40% of those early terminations were due to adverse events. A true and correct copy of this article from the *Archives of Internal Medicine* is attached hereto as Exhibit ML. Despite these early termination rates, tramadol, controlled release codeine and controlled release oxycodone have all been approved for marketing by the FDA.

16. Based on my work at Abbott, I am aware that since 2001 other pain compounds have been approved by the FDA for marketing despite experiencing high dropout rates in Phase II and/or Phase III clinical trials, and that Abbott relies upon this fact in its development of its own pain compounds. For example, I am aware that we have discussed at Abbott that in a Phase III clinical trial for AVINZA™, a pain drug that was approved in March 2002 by the FDA for the relief of moderate-to-severe pain, the blinded early termination rate was approximately 42% (87/205) and that approximately 26% of the patients at the highest dose dropped out due to adverse events.

17. I am currently working as a statistician on a pain compound in development at Abbott known as Vicodin Controlled Release ("Vicodin CR"). Vicodin CR is an opioid. Abbott recently completed a Phase II double-blinded, placebo-controlled clinical trial (M03-643) for Vicodin CR. I participated in the design of this study, in the preparation of the protocol, and in the analysis of the data from the study.

18. Based on my analysis in the ordinary course of my work for Abbott of the data from Abbott's M03-643 Vicodin CR study, I am aware that approximately 40% of the total number of randomized patients who participated in the trial (including active dose and placebo) failed to complete that trial (47% and 32%, respectively). I am also aware that 31% of the total number of randomized patients in the active treatment group

terminated early because of adverse events. Put another way, nearly 70% of the early terminations in the active treatment group were attributable to adverse events.

19. Based in part on the results of the M03-643 Vicodin CR Phase II study, which reached a statistically significant endpoint, Abbott decided to move forward into Phase III in the development of the compound.

20. More recently, Abbott completed a Phase III double-blinded, placebo-controlled clinical trial (M04-697) for Vicodin CR. I participated in the design of this pivotal Phase III study, in the preparation of the protocol, and in the analysis of the data from the study.

21. Based on my analysis in the ordinary course of my work for Abbott of the data from Abbott's M04-697 Vicodin CR Phase III study, which reached many statistically significant endpoints, I am aware that 45% of the patients who received Vicodin CR and 43% of the placebo patients dropped out of the study early. Of the 192 patients who received Vicodin CR in this study who dropped out early, more than half (100 patients) dropped out early because of adverse events.

22. I participated in the preparation and filing of the New Drug Application ("NDA") that Abbott recently submitted to the FDA for approval of Vicodin CR. Abbott's Vicodin CR NDA is based in part on the results of the M04-697 Phase III trial described above.

I declare under penalty of perjury, under the laws of the United States of America, that the foregoing is true and correct. Executed this 9th day of March 2008, at Grayslake, Illinois.

JAMES THOMAS

PART 1

ABBOTT LABORATORIES
Clinical Protocol

A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Protocol M99-114

February 8, 2000

Fred Siebert, MT-BB (ASCP)
Senior Clinical Research Associate, Analgesia Venture — 2/10/2000 Date

James Thomas for
David Morris, Ph.D.
Manager, Clinical Statistics — 2-11-00 Date

Walid M. Awni
Walid Awni, Ph.D.
Manager, Clinical Pharmacokinetics — 2/11/00 Date

Bruce G. McCarthy, M.D.
Associate Medical Director, Analgesia Venture — 2/10/00 Date

Christopher J. Silber, M.D.
Venture Head, Analgesia Venture — 2/10/00 Date

Abbott Laboratories

Thomas DEP. EX. NO. 5
FOR ID., AS OF 4/13/07

1.0 Title Page

Abbott Laboratories
Analgesia Venture, D48Q
Clinical Study

A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

ABT-594/M99-114
February 8, 2000

Development Phase: II

Investigators: Multicenter Trial

Estimated Date of First Subject to be Dosed: April 2000

Estimated Date of Last Subject to Complete Dosing: November 2000

Sponsor/Emergency Contact: Christopher J. Silber, M.D.
Venture Head,
Analgesia Venture
Phone: (847) 938-5236, Fax: (847) 938-5258
Department 48Q, Building AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193

This study will be conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

2.0 Study Synopsis

Name of Company: Abbott Laboratories **Name of Finished Product:** ABT-594 Hard Gelatin Capsule (HGC) **Name of Active Ingredient:** ABT-594	**Individual Study Table Referring to Part of the Dossier:** Not Applicable (N/A) **Volume:** N/A **Page:** N/A	*(For National Authority Use Only)*
Title of Study: A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter Study		
Study Center(s): 30		
Publication (reference): N/A		
Study Period (years): **Estimated Date of First Subject to be Dosed:** April, 2000 **Estimated Date of Last Subject to Complete Dosing:** November, 2000		**Phase of Development:** II
Objectives: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.		
Methodology: This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg, or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll 320 subjects who meet entry criteria for this study. Prior to any study-specific procedures at the Screening Visit, an informed consent will be signed and study eligibility determined.		

Methodology: (Continued)

Prior to study drug administration, subjects will have discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and have completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who meet entry criteria, will be randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Treatment Phase, subjects will return to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). During the Primer and Treatment Phases, subjects will be allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but will not be allowed to take acetaminophen within 24 hours prior to a Treatment Visit). Subjects will complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects will undergo site-based assessments of their neuropathy pain at the Baseline Visit and Treatment Visits I, II, III and IV. Subjects will discontinue study drug administration after Treatment Visit IV and return to the site for the Follow-Up visit 7-10 days later. See Figure 9.1a, Study Schematic, for additional study layout information.

Efficacy and safety assessments will include: the Pain Rating Scale (11-Point Likert), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change.

No. of Subjects: 320

Diagnosis and Main Criteria for Inclusion:

A subject may be randomized in this study provided that he/she meets all of the Inclusion Criteria outlined below and does not meet any of the Exclusion Criteria in Section 9.3.2.

- Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.
- The subject must be age 18 or older and in relatively good health with a recent stable medical history.
- The subject's weight must be ≤ 265 pounds.
- A female subject must be non-lactating and:
  - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),

    OR
  - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

  All female subjects must have a negative β subunit human chorionic gonadotropin (β-hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β-hCG at all Treatment Visits.
- The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.

- The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- The subject must have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) everyday during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

Test Product(s): ABT-594 75 µg HGC (Formulation A-2)

Dose: ABT-594 150 µg, 225 µg, or 300 µg BID (Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
ABT-594 75 µg HGC	58-293-AR

Duration of Treatment: 49 days

Reference Therapy: Placebo for ABT-594 HGC No. 1 Light Gray Opaque (Starch)

Dose: Placebo to match test product (see Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
Placebo for ABT-594 HGC	55-243-AR-01

Statistical Methods: (Continued)

Mean change from baseline to minimum, maximum and final values will be summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits will be flagged in the data listings. Furthermore, laboratory results which satisfy the criteria for limits for statistical analysis will be identified.

To assess dose proportionally and time invariance (from Visit I to Visit IV), dose-normalized C_{trough} and log-transformed dose-normalized AUC, and C_{max} from the subset of subject participating in intensive pharmacokinetic sampling will be subjected to a mixed effects model analysis with effects for dose level, visit, relevant covariates, and perhaps study center. The logarithmic transformation will be employed for AUC and C_{max}. An exploratory analysis will also be performed on the data set obtained from all subjects.

3.0 Table of Contents

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PART 2

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List of Tables

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List of Appendices

4.0 List of Abbreviations and Definitions of Terms

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or A-165594
CSI	Clinical Supplies Invoice
HGC	Hard Gelatin Capsules
IVRS	Interactive Voice Response System
nAChRs	Neuronal nicotinic acetylcholine receptors
NPRO	New Product Research Order
NPS	Neuropathic Pain Scale

5.0 Ethics

5.1 Institutional Review Board or Independent Ethics Committee

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator will obtain a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories will receive documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year. A complete list of documents required prior to initiation of the study is located in Appendix A.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version, Appendix B) and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix C.

5.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and

signed and dated by the subject and the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of an Informed Consent are specified in Appendix D.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study will identify each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the CRFs.

The site will collect information on the subject per International Council on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency should also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site according to the record retention guidelines outlined in Section 12.0.

Neither the subject, the subject's physician, nor the investigator will be informed of the subject's pharmacogenetic results, should they be obtained. If performed, results from individual subjects will be kept confidential and will not be given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples will be stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples will be kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Investigative sites will be selected by Abbott Laboratories. Approximately 30 sites will be selected to enroll subjects for this study.

6.2 Sponsor Information

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form will be generated by Abbott Laboratories. The database for this study will be created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories will be responsible for the statistical analysis of the data.

6.3 Contract Research Organization

Abbott Laboratories will delegate prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to a Contract Research Organization (CRO) for the conduct of this clinical study. The sponsor and CRO will maintain contact in order to manage adequately the progress of the study. The CRO will coordinate and perform all site visits and will prepare trip reports, using the Abbott format, for each visit performed. These reports will detail the activities conducted at all investigative sites and will include all relevant observations. All trip reports will be forwarded to the sponsor in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures (SOP).

6.4 Clinical Supply Management

Clinical supplies will be prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories will authorize the release of clinical supplies once the appropriate essential documents have been received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

All subjects will be centrally randomized by site and assigned to a treatment group (using a randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS will be contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using a randomization supplied by Abbott Laboratories) will also be assigned using IVRS. Each site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records (Appendix E), and records for return of used and unused clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) will check drug accountability records regularly.

6.5 Central Laboratory

This study will utilize one central laboratory contracted by, and under the direction of, Abbott Laboratories. All protocol specified clinical laboratory tests will be performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

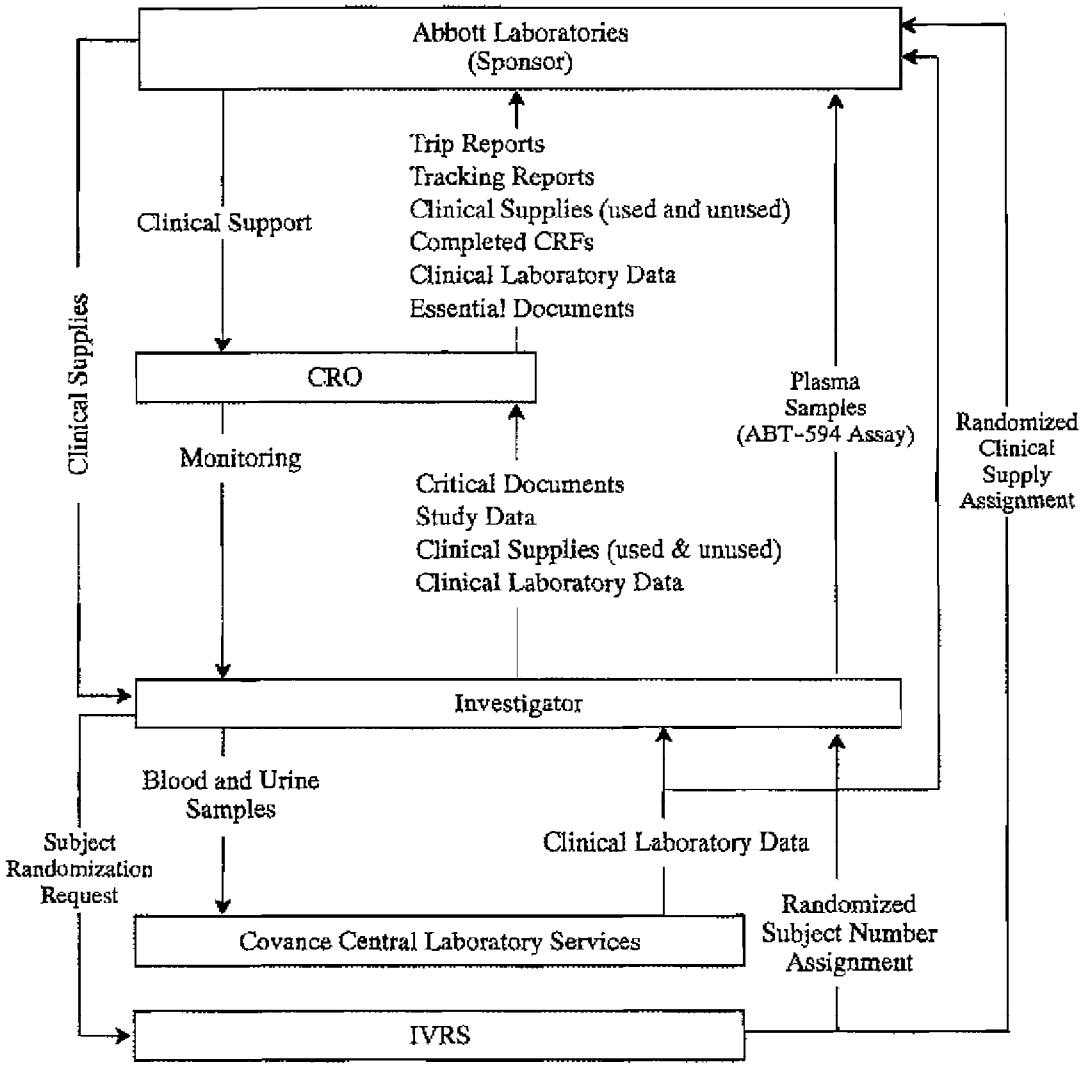

Figure 6.6a Administrative Structure

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.[1]

Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (±)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.[2] The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that

acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.[3] Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

Human clinical trials with ABT-594 began in 1997. Initial clinical trials were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 μg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Two Phase I studies with the HGC formulation have recently been completed: Study M99-076 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Ascending Doses of Twice Daily Dosing Regimens of a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects") and M99-120 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability and Pharmacokinetics of Escalating Doses of Twice Daily Dosing of a Hard Gelatin Capsule Formulation of ABT-594 in Adult Subjects in General Good Health"). Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 μg BID for 14 days. Study M99-120 included titrated doses up through 450 μg BID for 5 days. Adverse events, significantly different than placebo, for subjects receiving 300 μg BID for 14 days in Study M99-076 included: dizziness , nausea, vomiting, asthenia and diarrhea (all of which were considered to be mild in the opinion of the investigator). In addition, results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

Phase II has included (to date) efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon a study of molar extraction pain (Study M97-772, "A Randomized, Double-Blind, Single Dose Comparison of an Oral Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental Pain Model"), 100 μg ABT-594 (single dose oral solution) appeared to be a minimally efficacious dose in acute pain.

PART 3

A study of ABT-594 in osteoarthritis (Study M98-826, "A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain Associated with Osteoarthritis of the Knee") evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks and a study of ABT-594 in neuropathic pain (Study M98-833, "A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Patients with Painful Polyneuropathies") evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (greater than or equal to 5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature terminations).

Data from Phase I and II studies completed to date suggest that ABT-594 will be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, will be performed to test this hypothesis.

8.0 Study Objectives

The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll approximately 320 subjects who meet entry criteria for this study.

The study will be divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 is the first day of study drug administration. Subjects will be allowed a window of $\pm$ 3 days for each study visit. The study design is depicted in Figure 9.1a.

Subjects will review and sign the informed consent prior to the conduct of any study specific procedures. Subjects will then be screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclics, serotonin-specific reuptake inhibitors (SSRIs), anticpileptic drugs (AEDs), or other analgesics for the treatment of their pain must have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase (Day -7 to Day -1). During the Baseline Pain Assessment Phase, subjects will complete, at approximately 11 AM each morning, the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity. Subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7) during the Baseline Pain Assessment Phase.

On the day after the Baseline Pain Assessment Phase, subjects will return to the site for their Baseline Visit (Day 1). At this visit, diaries will be collected and reviewed. In addition, subjects will complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who meet all entry criteria, including an average of $\geq$ 4 points on the

diary-based Pain Rating Scale (11-Point Likert) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, will then complete the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects will undergo an interim medical history, physical examination, vital sign measurements, ECG and clinical laboratory tests.

Subjects who meet all entry criteria at the Baseline Visit will be randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID, or placebo. Subjects will start study drug at the evening dose on Day 1 (as specified in Section 9.4.5). During the Primer Phase, subjects randomized to ABT-594 will receive a fixed dose escalation of ABT-594 (as specified in Section 9.4.1). Following the Primer Phase, subjects will enter the Treatment Phase (Day 8) and will continue their treatment for a total of 49 days. During the Primer and Treatment Phases, subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7)

Subjects will complete the diary-based Pain Rating Scale each morning (approximately 11 AM), 3 hours after taking their morning dose of study drug. They will return to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV will include collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III) and efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute) (Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements and clinical laboratory tests (Treatment Visits I, III and IV), ABT-594 plasma assay collection (Treatment Visits I and IV only) and ECG (Treatment Visit IV only). A subset of subjects at selected sites will undergo intensive pharmacokinetic sampling at Treatment Visits I and IV.

On the day after Treatment Visit IV, subjects will enter the Post-Treatment Phase. Subjects will no longer take study drug or complete pain scales. Subjects may restart all discontinued medications under the guidance of their physician. Subjects will return for study procedures at the Follow-up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-up Visit will include physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participate in clinical studies of ABT-594 and who consent, a blood sample will be collected at Treatment Visit I in order to obtain a sample of genetic material (DNA). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

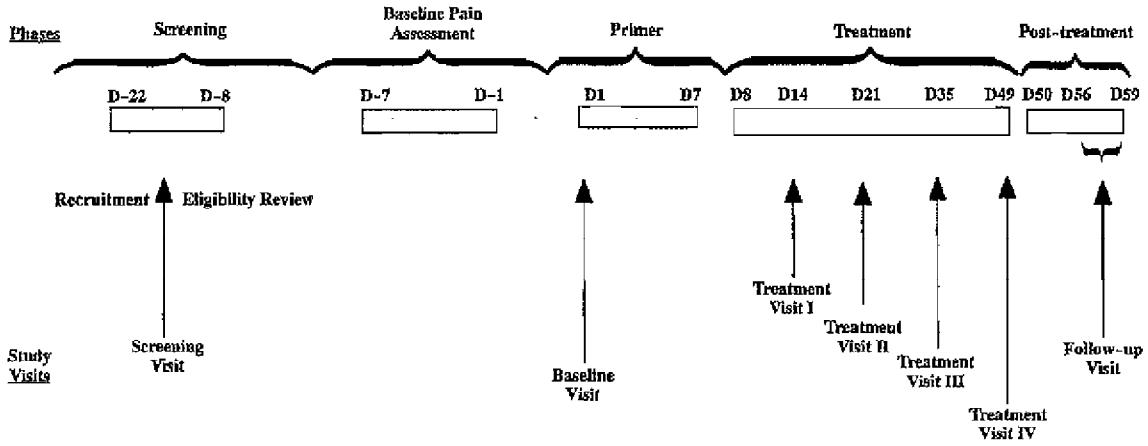

Figure 9.1a Study Schematic

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provides a placebo control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales will be employed.

9.3 Selection of Study Population

It is anticipated that approximately 320 subjects will be randomized and receive study medication in this study. A subject may be randomized in this study provided that he/she meets all of the inclusion criteria outlined in Section 9.3.1 and does not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

9.3.1.1 Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.

9.3.1.2 The subject must be age 18 or older and in relatively good health with a recent stable medical history.

9.3.1.3 The subject's weight must be ≤ 265 pounds.

9.3.1.4 A female subject must be non-lactating and:

- of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),

  OR

- of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative β subunit human chorionic gonadotropin (β-hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β-hCG at all Treatment Visits.

9.3.1.5 The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.

9.3.1.6 The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam **and** either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.

9.3.1.7 The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.

9.3.1.8 The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).

9.3.1.9 The subject must have an average of $\geq$ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and $\geq$ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

9.3.2.1 The subject has positive test results for drugs of abuse or viral hepatitis at the Screening Visit, or has a known history of a positive test result for HIV.

9.3.2.2 The subject has recent (< 5 years) history of drug or alcohol abuse or dependence.

9.3.2.3 The subject has an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.

9.3.2.4 The subject has active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that has been treated or other malignancies that have been surgically removed and have had no evidence of recurrence for a minimum of 5 years prior to study start).

9.3.2.5 The subject has taken an investigational drug within 1 month prior to administration of study treatment or is scheduled to receive an investigational drug other than ABT-594 during the course of this study.

9.3.2.6 The subject has a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.

9.3.2.7 The subject has orthostatic hypotension at the Screening Visit (as defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing), or a history of syncope or pre-syncopal symptoms.

9.3.2.8 The subject has previously participated in a study involving ABT-594, including the present study.

9.3.2.9 The subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including AST or ALT $\geq$ 1.5 times the upper limit of the reference range or a serum creatinine > 1.5 mg/dL. Subjects may have elevated serum and urine glucose, but their serum glucose must have been under good control (in the opinion of the investigator) for at least the last 3 months prior to the Screening visit.

9.3.2.10 The subject has clinically significant electrocardiographic abnormalities.

9.3.2.11 The subject has ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.

9.3.2.12 The subject has a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject cannot differentiate from the neuropathy pain.

9.3.2.13 The subject has sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.

9.3.2.14 The subject is unlikely to comply with the study protocol or is unsuitable for any other reason, in the opinion of the investigator.

9.3.3 Removal of Subjects from Therapy

A subject may voluntarily terminate participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to

terminate prematurely a subject's participation. The investigator must notify the CRA within 24 hours and document the reason for premature termination on the appropriate CRF.

Subjects, whose participation is terminated prematurely after signing study consent but before study drug administration, will not require follow-up observations. Subjects, whose participation is terminated prematurely after study drug administration must undergo procedures normally performed at Treatment Visit IV (see Table 9.5a) within 7-10 days following termination from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represents a significant risk to subjects, the study will be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID
ABT-594 225 µg BID
ABT-594 300 µg BID
Placebo for ABT-594 BID

ABT-594 and matching placebo will be supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects will receive a fixed dose escalation of ABT-594. ABT-594 will be initiated at 75 µg BID. The dose will increase every 2 days in 75 µg BID increments until subject are taking their assigned treatment dose (150, 225 or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4.1a.

Table 9.4.1a ABT-594 Dose Escalation

Treatment Regimen	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594	8 AM	[redacted]	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

Subjects will start study drug at PM dose on Day 1 (Section 9.4.5).

The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4.1b.

Table 9.4.1b Number and Type of Capsules by Treatment Regimen

Treatment Regimen	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg	2	2
ABT-594 225 µg	3	1
ABT-594 300 µg	4	0
Placebo	0	4

PART 4

9.4.2 Identity of Investigational Products

Table 9.4.2a Identity of Investigational Products

Test Preparation Drug Product	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR	52-015-KD-00	Abbott[1]
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	N/A	Abbott[1]

[1] Pilot Plant, North Chicago, Illinois

ABT-594 75 µg HGC and placebo HGC are identical in appearance, encapsulated in Light Gray Opaque capsule size No. 1 HGCs.

9.4.2.1 Packaging and Labeling

Study drug supplies will be blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards will be provided to each subject.

Daily study medication cards will be labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space will be provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies must be stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies must be stored at controlled room temperature (68-77°F, see USP).

9.4.2.3 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. Study drug will be dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who meets the enrollment criteria. The investigator or designee will record the subject number, subject initials and date dispensed to the subject on the Drug Accountability Form (Appendix E). The amount of study drug remaining will be recorded at Visits I, II, III and IV for each subject on the site Drug Accountability Form. An accurate running inventory of study drug will be kept and will include the NPRO number, CSI number(s), the number of modules dispensed and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for and returned to Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with the instructions of the CRA, will also be included in the shipment. The investigator agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects will be centrally randomized by investigative site using an Interactive Voice Response System (IVRS). Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site.

Approximately 320 subjects will be randomized in an equal ratio to receive either ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID or placebo. Subjects will be assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects will start study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects will then take BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs should be taken with at least one cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject will remain blinded to the subject's treatment throughout the course of the study. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) **MUST** be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. Blind breaking information will be provided using IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site. The sponsor must then be notified within 48 hours of the blind being broken. The date, and reason for blind breakage must be recorded on the appropriate CRF.

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks will be taken.

Concomitant analgesics (prescription or over-the-counter [OTC] except aspirin and acetaminophen as described below), including serotonin-specific reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, muscle relaxants, TENS and topical analgesics will not be allowed.

Aspirin, 325 mg daily maximum, is permitted if taken for primary prevention of thromboembolic events and the dose has been stable for ≥ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, is permitted. Subjects will not be allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline Visit and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication is necessary during the course of this study, the medication name, dosage information, frequency and dates of administration must be reported on the CRF. Concomitant analgesic medication use (frequency only) will be recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and Treatment Visits I, II, III and IV. The concomitant medication use record will include the number of separate occasions each subject has used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects will be instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance will be documented by the investigator or designee on the site Drug Accountability Form (Appendix E) and on the appropriate CRF.

Overdose information will be collected on the appropriate CRF.

9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures

9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Study procedures will be performed as summarized in Table 9.5a., Study Procedures Flow Chart.

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7		Treatment Phase D8-D49					Post-Treatment Phase D50-D59	
						Treatment Visit					
	Screening Visit		Baseline Visit D1	D2-D7	D8-D49	D14 I	D21 II	D35 III	D49 FV[a]		Follow-up Visit D56 to D59
Informed Consent	X										
Medical History	X		X[b]								
Physical Exam	X[c]		X						X		X
Vital Signs	X[d]		X[e]			X		X	X		X
ECG			X						X		X[f]
Clinical Laboratory Tests[g]	X		X			X		X	X		X[f]
Viral Hepatitis Screen	X										
Urine Drug and Alcohol Screen	X										
Pregnancy Test			X			X[h]	X[h]	X[h]	X[h]		
Genetic Polymorphism Sample (If Applicable)			X								
ABT-594 Plasma Assay						X			X		
ABT-594 PK Profile[i]						X			X		
Diary Issued	X		X			X	X	X			
Diary Collected			X			X	X	X	X		
Diary-Based Pain Rating Scale[j]		X		X	X						
Site-Based Pain Rating Scale			X			X	X	X	X		
Neuropathic Pain Scale			X			X	X	X	X		
Subject/Clinician Global Impression of Change									X		
SF-36™			X						X		
Randomize Patient			X								
Dispense Study Drug			X			X[k]	X	X			
Analgesic Use Monitoring			X			X	X	X	X		
Adverse Event Monitoring			X			X	X	X	X		X
Concomitant Medication Monitoring			X			X	X	X	X		X
Study Drug Accountability		X				X	X	X	X		

a Or upon premature termination.
b Interim history.
c Includes height.
d Includes orthostatic measurements at Screening Visit only.
e Includes oral temperature at Baseline Visit only.
f Performed only if there are clinically significant abnormalities at the previous evaluation.
g Chemistry, hematology and urinalysis.
h Required of all females of child-bearing potential.
i Study drug must be taken in front of study staff. Blood samples from selected subjects will be taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.
j To be completed at approximately 11 a.m., each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.
k Redispense D15-20 study medication after checking drug accountability.

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer will instruct the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) will be the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments include the diary-based and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale and the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements should be performed (when possible) 3-4 hours post dose.

Pain Rating Scale (11-Point Likert Scale)

Subjects will assess pain intensity daily by completing the Pain Rating Scale (Appendix F) in their diaries. These assessments will be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects will record the time they completed these assessments in their diaries.

Subjects will also assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments will be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature termination). The time of assessment will be recorded on the appropriate CRF.

Neuropathic Pain Scale

The Neuropathic Pain Scale (Appendix G) will be completed by subjects at the Baseline Visit and at Visits I, II, III, and IV (or upon premature termination).

Subject Global Impression of Change

The Subject Global Impression of Change (Appendix H) of analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

Clinician Global Impression of Change

The Clinician Global Impression of Change (Appendix H) of a subject's analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) will be completed by each subject at the Baseline Visit and at Treatment IV (or upon premature termination).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

Medical History

A complete medical history will be obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening will be recorded. The medical history will be updated at the Baseline Visit.

Physical Examination

A physical examination, including weight, will be performed at the Screening Visit, Baseline Visit, Treatment Visit IV and at the Follow-up Visit. Height will be measured at the Baseline Visit only. The physical examination performed at the Baseline Visit will serve as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate will be measured at the Screening Visit, Baseline Visit, Visits I, III, and IV and at the Follow-up Visit. Orthostatic blood pressure and pulse rate will be measured at the Screening Visit only. Oral temperature will be taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit will serve as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) should be obtained after the subject has been sitting for at least 3 minutes. Orthostatic measurements should be obtained after 3 minutes in the supine position and then after 1 minute in the standing position. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Subjects should not wear tight sleeves. Ideally, the subject's blood pressure should be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws. Subjects should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

Electrocardiogram (ECG)

A resting 12-lead ECG will be obtained at the Baseline Visit and Treatment Visit IV. An ECG will be performed at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The ECG performed at the Baseline Visit will serve as the baseline ECG.

A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples will be obtained for the laboratory tests listed in Table 9.5.b at the Screening Visit, Baseline Visit (Day 1), and Treatment Visits I, III, and IV. Laboratory tests will be obtained at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The laboratory test results obtained at the Baseline Visit will serve as the baseline results. Blood draws should be performed after pain assessments or vital sign determinations during a visit.

Table 9.5b Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total bilirubin	pH
White Blood Cell (WBC) count	Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)	Bilirubin
Neutrophils	Aspartate aminotransferase/serum glutamic-oxaloacetic transminase (AST/SGOT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Hemoglobin A_{1c} (Baseline Visit Only)	Chloride	
Lymphocytes	Calcium	
Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)	Inorganic phosphorus	
Platelet count (estimate not acceptable)	Uric Acid	
Prothrombin Time (PT)	Bicarbonate	
Partial Thromboplastin Time (PTT)	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

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The investigator will review all laboratory test results and will assess clinical significance for each abnormal result. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A copy of each laboratory report must be included with the CRF.

Viral Hepatitis Screen

Subjects will undergo serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody) at the Screening Visit. The hepatitis test panel will be performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens will be tested for drugs of abuse and alcohol at the Screening Visit and will be performed by the central laboratory.

Pregnancy Test

A urine pregnancy test will be performed by designated study personnel at the Baseline Visit for all female subjects and at Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female will not be eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected and unfavorable event such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of a drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject.

The subject will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken and all adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be reported on the appropriate CRF.

The investigator will assess and record any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known), severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

Table 9.5c Definitions for Investigator Rating of Adverse Event Severity

Rating	Definition
Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Rating	Definition
Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

Adverse events will be monitored continuously from the time of study drug administration to the Follow-up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature termination) will be collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects will be instructed to report to the investigator any other adverse events that occur after Follow-up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures that occur after signing the Informed Consent and prior to the first dose of study drug will also be collected.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

Ongoing medical conditions will be considered adverse events if there is an increase in severity or frequency of occurrence. Since measurements of pain intensity are efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study will not be considered adverse events for the purposes of this study.

Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to Abbott Laboratories as a serious adverse event (SAE) within 24 hours of occurrence or notification to the site:

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).

Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions will be reported to Abbott Laboratories as serious adverse events.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone, one of the following people at Abbott Laboratories within 24 hours of being made aware of any serious adverse event.

Bruce G. McCarthy, M.D.
Associate Medical Director
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193
Office: (847) 935-6244
Home: (773) 529-5729
Fax: (847) 938-5258

Christopher J. Silber, M.D.
Venture Head
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193
Office: (847) 938-5236
Home: (847) 615-0428
Fax: (847) 938-5258

Fred Siebert
Sr. Clinical Research Associate
Analgesia Venture
Dept. 48Q, Bldg. AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193
Office: (847) 938-1167
Home: (847) 298-4682
Fax: (847) 938-5258

In addition, a written confirmation of the occurrence, including any supplementary data, must be sent within 3 days of the telephone report to:

Bruce G. McCarthy, M.D.
Dept. 48Q, Bldg. AP34
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-6193
Fax: (847) 938-5258

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study are validated and are considered standard for this population. All clinical and laboratory procedures in this study are standard and generally accepted.

9.5.3 Efficacy Variables

All efficacy variables will be derived from the efficacy measurements (Section 9.5.1.1).

9.5.3.1 Primary Variable(s)

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variable(s)

Change from baseline to final and each scheduled evaluation will be calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert), change from baseline to each evaluation only
- Site Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health][4] PCS, and MCS.[5]

The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site.

9.5.4 Drug Concentration Measurements

9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay

Blood samples for ABT-594 plasma assay will be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) will be collected into a sodium heparin evacuated collection tube at each visit. Blood draws should be

performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinue, a blood sample will be taken for ABT-594 assay at the premature discontinuation visit, and the exact times at which the dose was taken will be recorded.

All blood samples will be immediately stored at 4°C or below. The samples will be separated by centrifugation within one hour after sample collection. The supernatant will be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information will also be recorded on the appropriate CRF. All labeled plastic vials will be placed in a rack to prevent breakage. **Plasma samples for determination of ABT-594 must be frozen at -5°C or colder within one hour from centrifugation.** All specimens will be kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the day of plasma assay blood draw, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draw will be recorded in the CRF.

9.5.4.2 Additional Pharmacokinetic Sampling

For those subjects participating in the additional pharmacokinetic sampling for PK profile (approximately 30 subjects), blood samples will be collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject will be instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication will be taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit should accommodate a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples will be collected as follows: just prior to dosing (0 hour)

and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects will receive their 8 PM dose as scheduled. Subjects will be confined at the site until the blood sample at the 8 hour time point is collected. Pharmacokinetic profile samples will be processed and stored as specified in Section 9.5.4.1 until shipment to Abbott Laboratories.

9.5.4.3 Shipment of Plasma Samples

An inventory list of the samples included in the shipment must accompany the shipment. The inventory list will include the shipping date, number of samples in the container, drug identification, Abbott protocol number, subject numbers, sample type, sampling times, and missing samples. The frozen samples will be packed in dry ice sufficient to last 2 days during shipping.

Arrangements will be made with Abbott Laboratories for shipping of the plasma samples to the following Abbott address:

Sample Receiving
Abbott Laboratories
Dept. 4TA, Bldg. AP9
100 Abbott Park Road
Abbott Park, IL 60064-6122
Phone: (847) 937-0889
Fax: (847) 938-9898

On the day of shipping, a copy of the inventory sheet should be faxed to the Sample Receiving Department at (847) 938-9898.

9.5.5 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples will be collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to

ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis will not be reported with the study summary. The samples may also be used for development of a diagnostic test for drug response.

The pharmacogenetic analyses involve two methods: one which examines known genes believed to be involved in the particular response (Candidate Gene), and one which uses a high density marker map to locate and identify genes related to the response (Genomic Association) by comparing the marker profile between the subjects with an effect and a corresponding negative control group. The Candidate Gene method includes genes related to drug metabolism, drug targets or target pathways, and others including genes relating to cellular homeostasis. The Genomic Association method utilizes a map of single nucleotide polymorphisms which by themselves are essentially meaningless, but when correlated with groups of two distinct subject groups allow the identification of the gene(s) related to the difference between the groups. For the purpose of pharmacogenetic studies such as this, the difference would be related to the response to the drug or the presence or absence of the disease being tested.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting will entail a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and be given a CRF completion workbook for reference. The CRAs will monitor each site approximately every 4 weeks. At each visit, 100% source-document review will be made against the entries on the CRFs and a quality-assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. The investigator must agree to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

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The SF-36™ Health Status Survey (Acute) will be recorded directly on the CRF and will be considered source data.

All CRFs must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the CRFs for completeness and accuracy and sign and date the set of case report forms where indicated.

Each CRF will be printed on 3-part NCR paper. The forms consist of a white, yellow and pink copy. The white and yellow copy of the completed, verified CRF will be collected by the CRA and the pink copy retained at the investigative site.

Data captured on the CRF will be entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF will be reviewed and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values, and any necessary corrections will be made to the database and documented via addenda or audit trail.

The laboratory results will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests will be 2-tailed and considered statistically significant if the P-value (Type 1 error rate) is less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons will be made as considered necessary. No statistical adjustments will be made for multiple comparisons.

The baseline for all variables (except for the diary-based Pain Rating Scale) will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses will be performed for 2 sets of data: intent-to-treat subjects and evaluable subjects. Subjects receiving at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert) will be included in the intent-to-treat analyses. The evaluable dataset will include subjects that receive at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses will be performed with all randomized subjects who receive at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements will be assessed. The analyses will be performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to r x c tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation will be calculated for all efficacy variables (except both Global Impression of Change scores).

Primary Efficacy Analysis

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable will be evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment group by study center interaction. If the interaction term is not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences will be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers have fewer than 1 subject per treatment group in the intent-to-treat dataset, data from such centers will be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert) score will be assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change will be analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS may also be analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation will be assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert). For the diary-based Pain Rating Scale (11-Point Likert), change from baseline to each scheduled evaluation will be analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change will be evaluated using CMH methodology on actual scores.

If indicated, exploratory analyses will be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

Dose response for ABT-594 will be explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites is not significant, then the nonparametric Jonckheere-Terpstra test will be used instead of Page's test to assess dose response of ABT-594.

Other analyses will be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, will be performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses will use the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis will have data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely terminate for lack of efficacy. The "observed cases" (OC) analysis will not estimate the missing evaluation, and a subject who does not have pain evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item will be calculated, when less than one-half (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

9.7.1.4 Safety Analyses

All subjects receiving at least 1 dose of study drug will be evaluated for safety.

Adverse events will be coded using the COSTART V[6] dictionary. Treatment-emergent adverse events (i.e., those which begin or worsen in severity after randomized study drug is taken) will be tabulated by body system and COSTART term for each treatment group. Treatment group differences will be evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, will be presented for each treatment group. Analyses by subgroup will be performed as appropriate.

Laboratory data will be analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses will be on the change from baseline to the minimum, maximum and final values during the study for each laboratory variable.

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) will be summarized.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory results which satisfy the criteria for limits for statistical analysis (Appendix I) will be identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG will be analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfy the criteria for below and above limits (Appendix I) will be identified.

Concurrent medication use will be summarized by treatment group.

Additional safety analyses will be performed as indicated.

9.7.2 Determination of Sample Size

The study is designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation is based on results obtained from Study M98-833 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy[7] and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

9.7.3 Pharmacokinetics/Pharmacodynamics

The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the trough plasma concentration (C_{trough}) will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) will be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{max}, dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{max} from the subset of subjects participating in the additional pharmacokinetic (PK) sampling will be subjected to a mixed effects model analysis. The model will include dose, visit (Visit I and Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine use status, and other variables that might account for variability in pharmacokinetics will be included as covariates. The study center factor will be included in the initial model, including a center main effect and, as appropriate, interaction of center with other factors. The center factor, or at least the interaction terms involving center, may be dropped from the model if they explain little of the variability in the data. If the number of subjects who have only Visit I data and not Visit IV data exceeds 20% of the subjects with intensive PK sampling, then analyses will also be performed for each visit separately. The hypothesis of invariance with dose will be tested by comparing the 300 µg BID dose vs the 150 µg BID dose. If the hypothesis of dose proportionality is rejected in a comparison, then the

225 µg BID dose will be compared to each of the 150 and 300 µg BID doses. If the visit by dose interaction is statistically significant, then a comparison will be made for each visit.

An exploratory analysis will also be performed on the data set obtained from all subjects (including those who do not participate in the intensive PK sampling). This analysis will appropriately take into account the time of sampling relative to dosing. The questions of dose proportionality and change from Visit I to Visit IV will be considered in this analysis.

If there is some evidence from the data of this study that ABT-594 is efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable will be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration will utilize the data of all subjects. An analysis using only the data of subjects undergoing intensive PK sampling may also be done. The model will include effects for efficacy variable baseline value and for visit. The center factor will be incorporated appropriately. The dependency of the measurements from the same subject will be accounted for.

Other analyses may be performed as necessary.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

This study will be conducted in accordance with the protocol, GCP, all applicable local, state federal regulations and regulatory requirements. Neither the investigator nor the CRO will modify this protocol without first obtaining the concurrence of Abbott Laboratories. The modification must be documented in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the subject or those of an administrative or clarifying nature, must be reviewed and approved by the Institutional Review Board before implementation. Abbott Laboratories must submit protocol amendments to the FDA and possibly to other government agencies.

This study will be terminated if these conditions are not met.

10.0 Protocol Deviations

When deviation from the protocol is deemed necessary for an individual subject, the investigator or other physician in attendance must contact the site study monitor at the CRO, who will contact Abbott Laboratories. Such contact will be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. Any departures from the protocol will be authorized only for that one subject.
A description of the departure from the protocol and the reason for it will be recorded on the CRF.

11.0 Use of Information and Publication

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 90 days before the date of submission to the intended publisher.

Neither the subject nor their physician will be informed of individual subject pharmacogenetic results, should they be performed, nor will anyone not directly involved in this research. This is due to the fact that, 1) the subject and their physician are already

aware of the subject's particular response to the drug and the study information would not affect their future medical care, and 2) if an association is established between a genetic sequence and a treatment response, separate studies must be conducted in order to validate or confirm the results and the properties of the test prior to the necessary regulatory approval to use the test for diagnostic purposes. DNA samples from this protocol may be used either for gene identification, validation, or diagnostic test development studies, as well as discovery of genes related to painful diabetic polyneuropathy.

12.0 Completion of The Study

The investigator will complete and report this study in satisfactory compliance with the protocol within 9 months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon in writing by both the investigator and Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are not pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____ _____
Signature of Principal Investigator Date

_____
Name of Principal Investigator (printed or typed)

PART 7

14.0 References

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Appendix A

Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott Laboratories has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed protocol for the study.
2. A signed Form FDA 1572 or equivalent document certifying the investigator's agreement to comply with U.S. Federal (21 CFR, ICH GCP Guidelines) regulations governing the conduct of the study.
3. A signed Abbott Financial Disclosure form.
4. A current curriculum vitae of the investigator. If sub-investigators will participate in the study, a curriculum vitae for each.
5. Requirements for the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
   - A copy of the letter of approval of the IRB/IEC. The letter must specify that both the protocol and consent form were approved.
   - The names and affiliations of the members of the IRB/IEC or assurance number.
   - If the principal and/or sub-investigator is a member of the IRB/IEC, a letter stating that he/she did not participate in the review or approval of the protocol or consent form.
6. A specimen copy of the IRB/IEC-approved informed consent document to be used in the study.
7. A list of normal ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
8. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

As a rule, these documents will be provided in the course of one or more visits to the investigator by an Abbott Laboratories representative. Usually the study cannot begin until all of the documents listed above have been provided.

Appendix B

Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,
35th World Medical Assembly, Venice, Italy, in October 1983,
41st World Medical Assembly, Hong Kong, in September 1989 and
48th General Assembly, Somerset West, Republic of South Africa 1996.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Appendix B (Cont.)

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

Appendix B (Cont.)

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obligated to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

Appendix B (Cont.)

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician - patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REASON FOR REVISION: Revised to correspond to the amendment adopted by the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa 1996.

Appendix C
Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott Laboratories are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is actually a form letter addressed to the sponsor (Abbott Laboratories), summarizing the investigators qualifications for the study and their willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. To secure prior approval of the study by an appropriate institutional review board which conforms to FDA regulations.
2. To make at least yearly reports on the progress of the study to the above committee, and a final report within three months of study completion.
3. To maintain current running records of the receipt, administration, and disposition of study medication and to return all unused study medication to Abbott Laboratories.
4. To obtain valid written informed consent from each patient who participates in the study.
5. To prepare and maintain adequate case histories of all persons entered into the study, including case report forms, hospital records, laboratory results, etc., and to maintain these data for a minimum of two years following notification by Abbott Laboratories that all investigations have been discontinued with this drug.
6. To identify all subinvestigators who will also supervise drug administration.
7. To report adverse effects to Abbott Laboratories promptly. In the event of serious or unexpected adverse event, to notify Abbott Laboratories immediately by telephone.
8. To allow possible inspection and copying by the FDA of case reports and records of drug distribution.

Appendix D
Elements of the Consent Form

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

For IND Studies, procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all patients participating in PPD Clinical Research studies or the patients' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of patients involved in the trial.
4. The expected duration of the patient's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The patient's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the patient and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the patient for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the patient, this should be stated.

Appendix D (Cont.)

13. The anticipated prorated payment, if any, to the patient for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
15. A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research patient's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the patient.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the patients' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the patient or the patient's legally acceptable representative is authorizing such access.
21. A statement that the site will collect information on the patient per ICH requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency will also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site.
22. A statement that the records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the patients' participation in the trial may be terminated.

Appendix D (Cont.)

24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the patient may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the consent is given to the patient.
29. The statement, "I agree to participate..."
30. A place for the patient or the patient's legally acceptable representative to sign and date.
31. A place for the person who conducted the informed consent discussion to sign and date.

PART 8

Appendix E
Sample Abbott Laboratories Drug Accountability Form
Study M99-114

Subject Randomization Number:◆ _____ **Subject Initials:** _____ **Subject Birthdate:** _____

Investigator's Name: _____ **Location:** _____

	Module Carton Type	Module # ◆	NPRO #	Clinical Supplies Invoice No.	Date Received (M/D/Y)
Baseline Visit	Days 1-7				
Baseline Visit	Days 8-49				
Visit II	Days 8-49				
Visit III	Days 8-49				

Visit	DISPENSED TO SUBJECT					RETURNED FROM SUBJECT			VERIFIED BY CRA	
	Module # ◆	# Capsules	Date	By*	Checked By	Date	No. of Capsules Remaining	By*	By+	Date
Baseline Visit	Days 1-7	52								
	__ __ __ __ __									
	Days 8-49	144								
	__ __ __ __ __									
Visit I	Redispense balance of Days 8-49 cards remaining from Baseline Visit									
	__ __ __									
Visit II	__ __ __ __ __	144								
Visit III	__ __ __ __ __	144								

* Pharmacist/Coordinator/Nurse + CRO Monitor ◆ Assigned by IVRS

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Appendix F
Pain Assessments

Pain Rating Scale (11 point Likert)

The subject's pain intensity will be assessed by completion of the following statement in the daily diaries and at the investigative site.

How severe was your neuropathy pain during the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Possible

Appendix G

Neuropathic Pain Scale

Instructions: There are several different aspects of pain which we are interested in measuring: pain **sharpness, heat/cold, dullness, intensity,** overall **unpleasantness,** and **surface vs. deep** pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."

Not sharp	0	1	2	3	4	5	6	7	8	9	10	The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain feels. Words used to describe very hot pain include "burning" and "on fire."

Not hot	0	1	2	3	4	5	6	7	8	9	10	The most **hot** sensation imaginable ("on fire")

4. Please use the scale below to tell us how **dull** your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most **dull** sensation imaginable

Appendix G (Cont.)

5. Please use the scale below to tell us how **cold** your pain feels. Words used to describe very cold pain include "like ice," and "freezing."

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most **itchy** sensation imaginable ("like poison oak")

8. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how **unpleasant** your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most **unpleasant** sensation imaginable ("intolerable")

9. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No **deep** pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense deep** pain sensation imaginable

10. **HOW INTENSE IS YOUR *SURFACE* PAIN?**

No **surface** pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense surface** pain sensation imaginable

Appendix H
Subject Global Impression of Change and Clinician Global Impression of Change

Subject Global Impression of Change

The subject's impression of pain relief will be assessed by completion of the following statement:

Compared to the Baseline Pain Assessment Phase, how much have you changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

Clinician Global Impression of Change

The clinicians impression of pain relief will be assessed by completion of the following statement:

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to Baseline, how much has the subject changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

Appendix I
Laboratory Determinations, Vital Signs and Electrocardiogram Variables for Statistical Analysis

Hematology	Below Limit	Above Limit
Hemoglobin (g/dL)		
Female	$\leq$ 9.5	$\geq$ 16.5
Male	$\leq$ 11.5	$\geq$ 18.5
Hematocrit (%)		
Female	$\leq$ 32	$\geq$ 50
Male	$\leq$ 37	$\geq$ 55
Red Blood Cells (x 10^{12}/L)		
Female	$\leq$ 3.5	$\geq$ 6.0
Male	$\leq$ 3.8	$\geq$ 7.0
White Blood Cells (x 10^9/L)	$\leq$ 2.8	$\geq$ 16.0
Platelet Count (x 10^9/L)	$\leq$ 75	$\geq$ 700
Eosinophils (%)		$\geq$ 10
Basophils (%)		$\geq$ 10
Lymphocytes (%)		$\geq$ 75
Monocytes (%)		$\geq$ 15
Neutrophils (%)	$\leq$ 15	
Bands (%)		$\geq$ 10
Mean Corpuscular Volume (fL)	$\leq$ 0.8 x LLN	$\geq$ 1.2 x ULN
Mean Corpuscular Hemoglobin Concentration (g/dL)	$\leq$ 0.8 x LLN	$\geq$ 1.2 x ULN
Atypical Lymphocytes (%)		$\geq$ 5
Prothrombin Time (sec)		$\geq$ 2 ULN
Partial Thromboplastin Time (sec)		$\geq$ 2 ULN

LLN = Lower limit of normal ULN = Upper limit of normal

Appendix I (Cont.)

Chemistry	Below Limit	Above Limit
Albumin (g/dL)	≤ 2.5	
Alkaline Phosphatase (IU/L)		≥ 3 x ULN
Bicarbonate (mEq/L)	≤ 12	≥ 38
BUN (mg/dL)		≥ 30
Calcium (mg/dL)	≤ 8.2	≥ 12
Chloride (mEq/L)	≤ 90	≥ 118
Cholesterol (mg/dL)		≥ 600
Creatinine (mg/dL)		≥ 2.0
Direct Bilirubin (mg/dL)		≥ 2.0
Glucose (mg/dL)	≤ 45	≥ 175
LDH (IU/L)		≥ 3 x ULN
Inorganic Phosphorus (mg/dL)	≤ 1.7	≥ 5.5
Potassium (mEq/L)	≤ 3.0	≥ 6.0
SGOT/AST (IU/L)		≥ 3 x ULN
SGPT/ALT (IU/L)		≥ 3 x ULN
Sodium (mEq/L)	≤ 126	≥ 156
Total Bilirubin (mg/dL)		≥ 2.0
Total Protein (g/dL)	≤ 4.5	≥ 10
Triglycerides (mg/dL)		≥ 600
Uric acid (mg/dL)		
Female		≥ 8.5
Male		≥ 10.5

ULN = Upper limit of normal

Appendix I (Cont.)

Urinalysis	Below Limit	Above Limit
Specific Gravity	≤ 1.001	≥ 1.030
PH	≤ 4	≥ 9
Protein		≥ 3+* (≥ 10)
Ketones		≥ 3+*
RBC		
Female		≥ 10/hpf
Male		≥ 8/hpf
WBC		≥ 10/hpf (≥ 2+)
Casts		≥ 9
Glucose		≥ 3+*
Oral Body Temperature		
Temperature	Low: decreased ≥ 2°F from baseline	
	High: ≥ 101°F	
Body Weight		
Weight	Low: decreased ≥ 15% from baseline	
	High: increased ≥ 15% from baseline	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mmHg and decreased ≥ 30 from baseline	
	High: ≥ 180 mmHg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mmHg and decreased ≥ 20 from baseline	
	High: ≥ 105 mmHg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline	
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	

* ≥ 3+ on a scale with 4+ being the maximum value

Appendix I (Cont.)

Electrocardiogram	
PR Interval	High: ≥ 210 msec
QRS Duration	Low: ≤ 50 msec High: ≥ 150 msec
QT Interval	Low: ≤ 200 msec High: ≥ 500 msec
QTc Interval*	Low: ≤ 200 msec High: ≥ 500 msec
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline

* QTc calculated as QT divided by the square root of RR interval